



## EFFECTS OF EXPOSURE TO DIFFERENT TYPES OF RADIATION ON BEHAVIORS MEDIATED BY PERIPHERAL OR CENTRAL SYSTEMS

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### ABSTRACT

The effects of exposure to ionizing radiation on behavior may result from effects on peripheral or on central systems. For behavioral endpoints that are mediated by peripheral systems (*e.g.*, radiation-induced conditioned taste aversion or vomiting), the behavioral effects of exposure to heavy particles ( $^{56}\text{Fe}$ , 600 MeV/n) are qualitatively similar to the effects of exposure to gamma radiation ( $^{60}\text{Co}$ ) and to fission spectrum neutrons. For these endpoints, the only differences between the different types of radiation are in terms of relative behavioral effectiveness. For behavioral endpoints that are mediated by central systems (*e.g.*, amphetamine-induced taste aversion learning), the effects of exposure to  $^{56}\text{Fe}$  particles are not seen following exposure to lower LET gamma rays or fission spectrum neutrons. These results indicate that the effects of exposure to heavy particles on behavioral endpoints cannot necessarily be extrapolated from studies using gamma rays, but require the use of heavy particles.

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### INTRODUCTION

Exposing an organism to ionizing radiation can produce a variety of deleterious effects at both the cellular and organismic levels. At the cellular level, ionizing radiation has been reported to produce chromosomal aberrations, cellular inactivation and carcinogenesis (*e.g.*, Ainsworth, 1986; Hüttermann *et al.* 1989; Kraft *et al.* 1989; Leith *et al.* 1986). At the organismic level, exposure to radiation can produce taste aversion (CTA) learning and emesis (Rabin *et al.* 1989; 1991; 1992). These particular cellular and organismic effects are seen following exposure to low linear energy transfer (LET) types of radiation, such as  $^{60}\text{Co}$  gamma rays and following exposure to high LET heavy particles, such as iron ( $^{56}\text{Fe}$ ).

For biological endpoints, the general finding has been that the effects of exposure to both low LET and high LET types of radiation are qualitatively similar. The major difference between these types of radiation is in terms of the relative biological effectiveness (RBE) of the radiation: the effectiveness with which exposure to the radiation affects on the specific endpoints under consideration. Past research with these biological endpoints has shown that the effects of exposure to heavy particles are qualitatively similar to the effects of exposure to low LET types of radiation. The major difference seems to be that high LET heavy particles are generally more effective in producing alterations in these biological

endpoints than is exposure to other types of radiation (Ainsworth, 1986; Hüttermann *et al.* 1989; Kraft *et al.* 1989; Leith *et al.* 1986). Because of this, results of studies of the effects of exposure to low LET gamma radiation has been taken as the basis for extrapolation to the effects of heavy particles (*e.g.*, Bogo, 1988; Bogo and Ward, 1991).

While the qualitative similarity of the effects resulting from both low and high LET irradiation has been established for many biological endpoints, it remains to be completely determined whether or not a similar relationship obtains for behavioral endpoints. An additional unknown for behavioral endpoints derives from the fact that exposure to ionizing radiation can produce effects on either peripheral or central systems, or both. The experiments reviewed and reported here are concerned with a consideration of whether or not different behavioral endpoints, like biological endpoints, show a continuity between the effects of exposure to low LET types of radiation and to exposure to heavy particles.

## METHODS

The behavioral endpoint for all the studies reported here was the CTA. A CTA is produced when a novel tasting solution is paired with a toxic unconditioned stimulus. As a result of that pairing, the organism will avoid ingestion of that solution at a subsequent presentation. The CTA is the standard procedure for assessing the behavioral toxicity of a variety of stimuli, including radiation and chemical compounds (Rabin and Hunt, 1986; Riley and Tuck, 1985).

Taste aversions were produced by exposing rats to different types of ionizing radiation or to injection of chemical compounds. Using sources at the Armed Forces Radiobiology Research Institute, rats were exposed to  $^{60}\text{Co}$  gamma rays or fission spectrum neutrons ( $n^0$ ). Rats were exposed to 600 MeV/n  $^{56}\text{Fe}$  particles using the BEVALAC at Lawrence Berkeley Laboratory. The chemical compounds which were used to produce a CTA were lithium chloride ( $\text{LiCl}$ , 1.5 mEq/kg, i.p.) and amphetamine (3 mg/kg, i.p.). The general procedure for producing a CTA is shown in Figure 1.

## Taste Aversion Learning

Adaptation	Conditioning	Test
30 Min Water/Day	30 Min 10% Sucrose (Conditioned Stimulus) <div style="text-align: center;">↓</div> Irradiation or Chemical Toxin (Unconditioned Stimulus)	30 Min 10% Sucrose

- Data: 1) Preference Score = Sucrose intake/Total fluid intake  
 2) Test day intake as a percentage of conditioning day intake

Fig. 1. Procedure for producing a CTA.

## RESULTS AND DISCUSSION

### Radiation-Induced CTA Learning

The effects of exposure to different types of radiation are shown in Figure 2, which presents the dose/response curves for  $^{60}\text{Co}$  gamma rays, fission spectrum neutrons, and  $^{56}\text{Fe}$  particles. These curves show that for all types of radiation, the acquisition of a CTA is dose-dependent; such that increasing the dose causes an increase in the avoidance of the normally preferred sucrose solution. Of the three types of radiation,  $^{60}\text{Co}$  gamma rays are the least effective in producing a CTA. Exposure to fission spectrum neutrons is significantly more effective in producing a CTA than is exposure to  $^{60}\text{Co}$ . In turn,  $^{56}\text{Fe}$  particles are the most behaviorally toxic type of radiation, having the lowest threshold dose for the acquisition of a CTA and the lowest dose which produces maximal suppression of sucrose intake. In terms of RBE (Figure 3), these results suggest a continuum, in which the effectiveness of a specific type of radiation in leading to the acquisition of a CTA is related to LET, such that progressively higher LET is correlated with increased RBE.

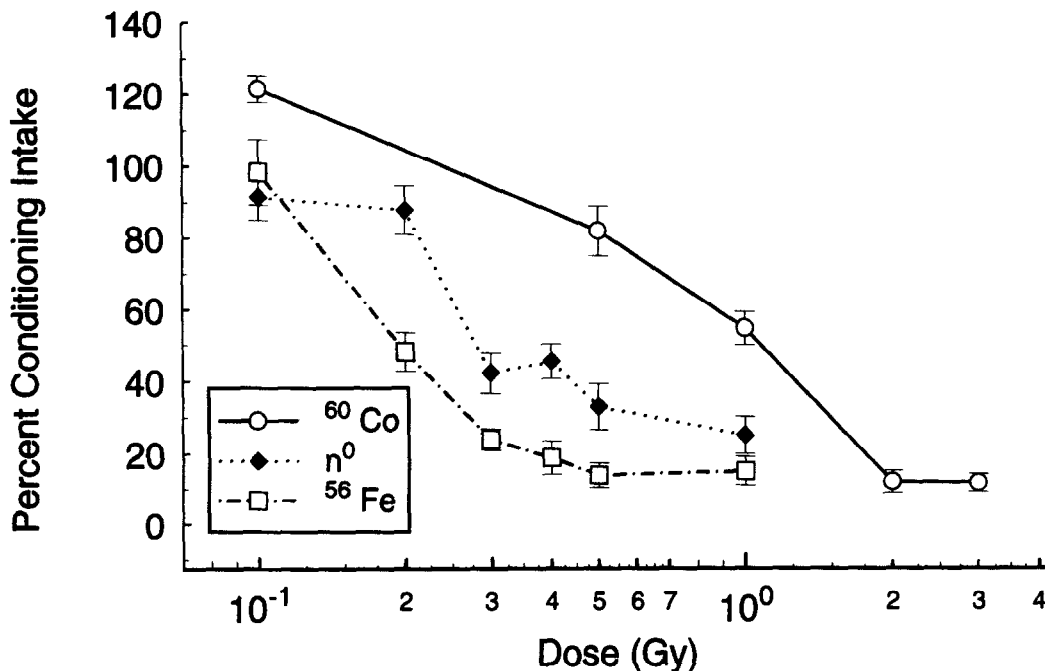


Fig. 2. Dose-response curves for the acquisition of a CTA following exposure to cobalt-60 gamma rays ( $^{60}\text{Co}$ ), fission spectrum neutrons ( $n^0$ ) or iron-56 particles ( $^{56}\text{Fe}$ ). Redrawn from Rabin *et al.* (1989).

Previous research (*e.g.*, Rabin *et al.* 1983) has established that the acquisition of a radiation-induced CTA is dependent upon the integrity of the area postrema (AP), the chemoreceptive trigger zone for emesis (Borison, 1974). The AP is a highly vascularized circumventricular organ which is characterized by a weak blood-brain barrier. CTA learning produced by treatment

with toxic compounds which do not cross the blood-brain barrier themselves, or which affect the organism by means of effects on peripheral systems are disrupted by lesions of the AP (Berger, 1974; Smith, 1980). To the contrary, stimuli that produce CTA learning through a central nervous system locus of action are not affected by lesions of the AP (Rabin and Hunt,

1986). Therefore, the observation that lesions of the AP disrupt the acquisition of a  $^{60}\text{Co}$ -induced CTA provides evidence for a peripheral mode of action for  $^{60}\text{Co}$  in the production of a CTA, probably through the effects of irradiation on the gastrointestinal system. Consistent with this interpretation is the observation that body-only  $^{60}\text{Co}$  exposures are significantly more effective in producing CTA learning than are head-only exposures (Rabin *et al.* 1984). The observation that lesions of the AP are equally effective in disrupting  $^{56}\text{Fe}$ -induced CTA learning (Rabin *et al.* 1989) indicates that  $^{56}\text{Fe}$ -induced CTA learning results from the operation of similar AP-dependent mechanisms. Thus, the CTA produced by exposure to either  $^{60}\text{Co}$  gamma rays or  $^{56}\text{Fe}$  particles results from the effects of the exposure of peripheral systems.

The results of these experiments indicate that for a behavioral endpoint which depends upon the effects of radiation on peripheral systems, the relative effectiveness of different types of radiation forms a continuum (Figure 3). The behavioral effects of exposure to heavy particles and other types of radiation are qualitatively similar. The differences between  $^{60}\text{Co}$  gamma rays, fission spectrum neutrons and  $^{56}\text{Fe}$  particles are observed as quantitative differences in RBE. As the LET of the radiation increases, there is a corresponding increase in RBE. For behaviors mediated by the effects of the radiation on peripheral systems, therefore, it is possible to extrapolate from the results obtained by exposure to low LET radiation to heavy particles.

### Amphetamine-Induced CTA Learning

Despite the fact that it is often self administered, amphetamine will also produce a CTA (Hunt and Amit, 1987). Because amphetamine is a dopamine agonist which readily crosses the blood-brain barrier, the CTA produced by injection of amphetamine results mainly from a central action of the drug at dopaminergic synapses (Carr and White, 1986). Support for this hypothesis is provided by the observation that lesions of the AP are not completely effective in preventing the acquisition of a CTA produced by injection of amphetamine (3 mg/kg) in rats (Rabin and Hunt, 1989; Ritter *et al.* 1980). Similarly, pretreating rats with the dopamine antagonist haloperidol (0.5 mg/kg, i.p.) attenuates amphetamine-induced CTA learning (Rabin and Hunt, 1989). In contrast, AP lesions are effective in attenuating the peripherally mediated CTA produced by injection of LiCl or ionizing radiation (Rabin and Hunt, 1989); whereas pretreatment with haloperidol has no effect on the acquisition of a LiCl- or radiation-induced CTA (Rabin and Hunt, unpublished data).

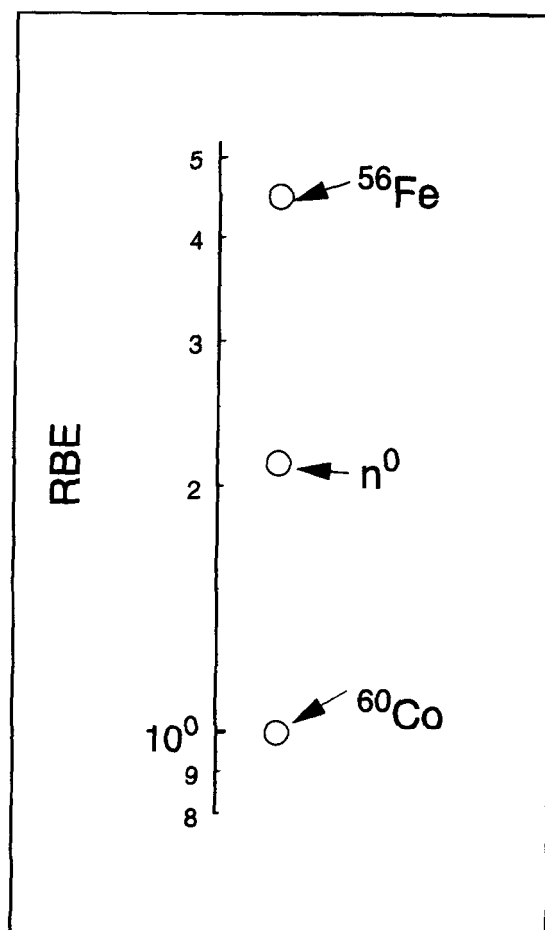


Fig. 3. Relative biological effectiveness (RBE) of different types of radiation in producing CTA learning in rats. Abbreviations as in Fig. 2. Redrawn from Rabin *et al.* (1992).

Work by Joseph *et al.* (1992; 1993) has shown that exposing rats to low doses (0.1-1.0 Gy) of  $^{56}\text{Fe}$  particles affects the functioning of dopaminergic neurons in the striatum and the motor behavior that depends upon the integrity of this system. This observation suggested the possibility that exposure to low doses of  $^{56}\text{Fe}$  particles might also disrupt other behaviors which depend upon the integrity of the dopaminergic system, specifically amphetamine-induced CTA learning.

Three days following exposure to 600 MeV/n  $^{56}\text{Fe}$  particles (0.0, 0.1, 0.5 or 1.0 Gy) rats were administered either amphetamine (3 mg/kg, i.p.) or LiCl (1.5 mEq/kg, i.p.) using the CTA procedure detailed above. Compared to sham irradiated controls, all rats exposed to  $^{56}\text{Fe}$  particles showed a significantly reduced CTA following injection of amphetamine (Figure 4A). Exposing rats to these doses of  $^{56}\text{Fe}$  particles had no effect on the acquisition of an LiCl-induced CTA. As shown in the inset (Figure 4B), pretreatment with the dopamine antagonist haloperidol also disrupts the acquisition of an amphetamine-induced CTA, but has no effect on the acquisition of an LiCl-induced CTA. Because the acquisition of a CTA produced by injection of amphetamine, but not by injection of LiCl, depends upon the integrity of the central dopaminergic system, these results are consistent with the hypothesis that the disruption of amphetamine-induced CTA learning by exposure to low doses of  $^{56}\text{Fe}$  particles is due to a direct effect on dopaminergic mechanisms in the central nervous system.

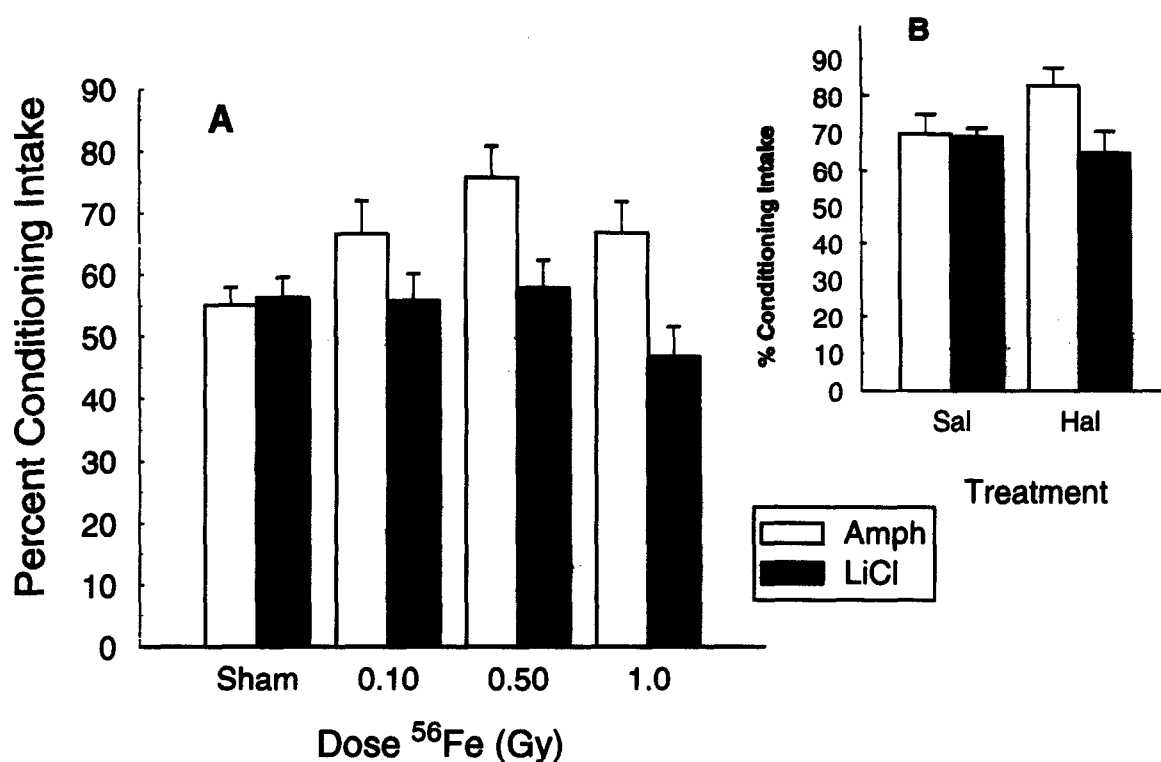


Fig. 4. A. Effect of exposure to  $^{56}\text{Fe}$  particles on the acquisition of an amphetamine (Amph)- or LiCl-induced CTA. B. Effect of pretreatment with saline (Sal) or haloperidol (Hal) on amphetamine- or LiCl-induced CTA learning. Redrawn with additional data from Rabin *et al.* 1994.

Because the effects of lesions of the AP identical for  $^{56}\text{Fe}$ - and for  $^{60}\text{Co}$ -induced CTA learning (Rabin *et al.* 1989), it was decided to determine whether or not exposure to  $^{60}\text{Co}$  would produce similar selective

effects on a dopamine-mediated behavior. Although there might be differences in RBE following exposure to  $^{56}\text{Fe}$  particles or to  $^{60}\text{Co}$  gamma rays, if the mechanisms by which exposure these types of radiation are similar, then the behavioral effects of exposure should be similar. The results are summarized in Figure 5. In contrast to the results obtained following exposure to doses of  $^{56}\text{Fe}$  particles as low as 0.10 Gy, exposing rats to doses of up to 9 Gy of  $^{60}\text{Co}$  gamma rays did not have selective effects on the acquisition of an amphetamine-induced CTA. Rather, at the 9 Gy dose, there was a non-selective decrease in both LiCl- and amphetamine-induced CTA learning. This observation suggests that the high dose of  $^{60}\text{Co}$  gamma rays did not have specific effects on the dopaminergic system, as observed with  $^{56}\text{Fe}$  particles, but rather produced a non-specific radiation-induced illness that affect all types of behavior.

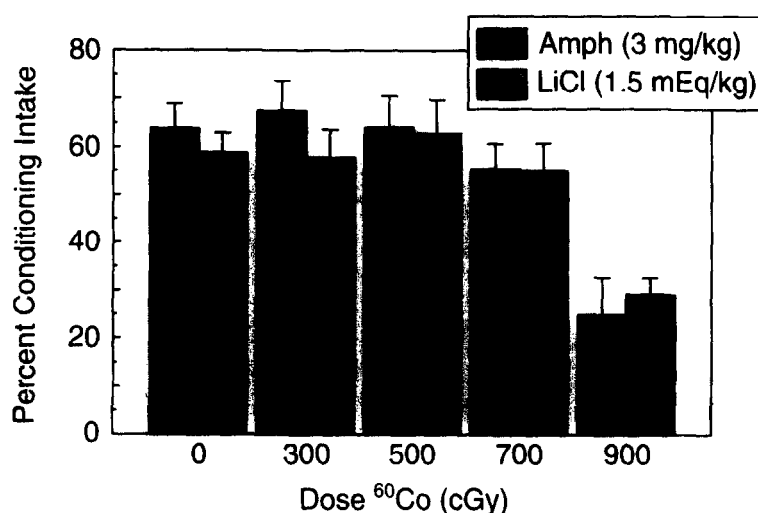


Fig. 5. Effects of exposure to  $^{60}\text{Co}$  gamma rays on the acquisition of amphetamine- and LiCl-induced CTA learning. Redrawn with additional data from Rabin *et al.* (1994).

The LET of  $^{60}\text{Co}$  gamma rays is  $\approx 0.3 \text{ keV}/\mu\text{m}$  compared to an LET of  $\approx 189 \text{ keV}/\mu\text{m}$  for 600 MeV/n  $^{56}\text{Fe}$  particles. While it is possible this difference in LET accounted for the observed differences in the effects of exposure on the dopaminergic system and on dopamine-mediated CTA learning, it is also possible that the behavioral effects of exposure to heavy particles are qualitatively different from the effects produced by exposure to other types of radiation. To evaluate this possibility, rats were exposed to fission spectrum neutrons, which have an LET of  $\approx 65 \text{ keV}/\mu\text{m}$ , using the procedures described above. As observed following  $^{60}\text{Co}$  irradiation, exposing rats to doses of up to 3 Gy of fission spectrum neutrons (Figure 6) did not produce a selective impairment in the acquisition of an amphetamine-induced CTA. Rather there was a non-selective decrease in test day sucrose intake following injection of isotonic saline as well as following injection of amphetamine or LiCl. These observations are consistent with the interpretation that exposure to 3 Gy of fission spectrum neutrons produces a generalized impairment of all behavioral functioning and not the selective impairment of dopaminergic-mediated behaviors observed following exposure to  $^{56}\text{Fe}$  particles. Because injection of isotonic saline does not typically lead to the acquisition of a CTA (*e.g.*, Rabin and Hunt, 1986), the observation of decreased sucrose intake in response to injection of isotonic saline following exposure to 3 Gy of  $n^0$  further supports the interpretation of a generalized radiation-induced illness rather than the specific disruption of the dopamine-mediated CTA.

Exposing rats to 9 Gy of  $^{60}\text{Co}$  gamma rays or 3 Gy of fission neutrons produced a non-selective disruption of CTA learning produced by both amphetamine and LiCl. Exposing rats to lower doses of  $^{60}\text{Co}$  or  $n^0$  has no effect on the acquisition of a CTA produced by injection of either amphetamine or LiCl. Thus, a comparison of the effect of exposure to  $^{60}\text{Co}$  gamma rays with those of fission spectrum neutrons indicates that LET may not be a factor in the selective disruption of dopaminergic function in amphetamine-induced CTA learning produced by exposure to  $^{56}\text{Fe}$  particles. Rather, the observation that the non-selective impairment of both amphetamine- and LiCl-induced CTA learning occurred following exposure to only 3 Gy of  $n^0$  compared to 9 Gy for  $^{60}\text{Co}$ , is consistent with the higher RBE of fission spectrum neutrons for a range of other biological endpoints (Ainsworth, 1986; Hüttermann *et al.* 1989; Kraft *et al.* 1989; Leith *et al.* 1986; Rabin *et al.* 1989, 1992). For the behavioral endpoints used in the present experiments, the effect of LET *per se* is seen in the dose needed to produce a generalized disruption of sucrose intake following treatment with either LiCl or amphetamine.

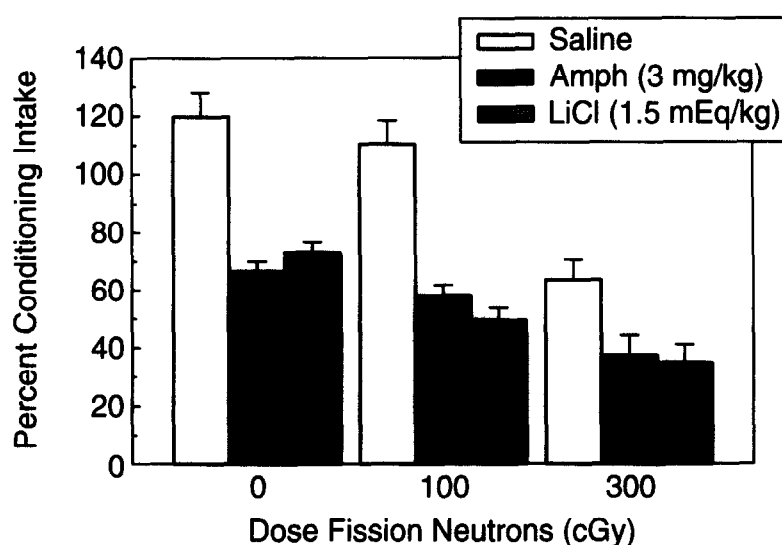


Fig. 6. Effects of exposure to fission spectrum neutrons on the acquisition of amphetamine- and LiCl-induced CTA learning. Redrawn with additional data from Rabin *et al.* (1994).

The results of these three experiments support the hypothesis that the behavioral effects of exposure to heavy particles (specifically  $^{56}\text{Fe}$ ) are qualitatively different than those observed following exposure to other types of radiation ( $^{60}\text{Co}$  or  $n^0$ ) when the endpoint is mediated by direct effects of irradiation on the central nervous system. Exposing rats to low doses of  $^{56}\text{Fe}$  particles produced a disruption of dopaminergic function as measured by the capacity of amphetamine to elicit a dopamine-mediated CTA. The disruption of CTA learning was restricted to use of amphetamine as the unconditioned stimulus and was not observed with LiCl as the unconditioned stimulus. This effect was not seen following exposure to types of radiation other than the  $^{56}\text{Fe}$  particles despite the fact that doses used with  $^{60}\text{Co}$  gamma rays was greater by a factor of nearly 100. These results are consistent with the neurochemical studies of Joseph *et al.* (1992; 1993; unpublished results) which show a disruption of dopaminergic function in the striatum of rats only following exposure to  $^{56}\text{Fe}$  particles and not following exposure to  $^{60}\text{Co}$  gamma rays or fission spectrum neutrons.

## CONCLUSIONS

Exposing an organism to ionizing radiation can affect a variety of physiological systems, both peripheral and central. This, in turn has implications for the effects of exposure on behavior. Radiation-induced CTA learning following exposure to  $^{60}\text{Co}$  gamma rays, fission spectrum neutrons or  $^{56}\text{Fe}$  particles is mediated by the effects of exposure on peripheral systems, primarily the gastrointestinal system. The physiological mechanisms underlying this behavior do not vary as a function of the type of radiation. The effects of exposure to  $^{60}\text{Co}$  or  $n^0$  are qualitatively similar to those of heavy particles ( $^{56}\text{Fe}$ ) on this system, differing only in the relative effectiveness with which the different types of radiation produce their effect on behavior. As such, it is possible to extrapolate from the effects of exposure to gamma rays or fission spectrum neutrons to effects obtained following exposure to heavy particles. In contrast, for behaviors mediated by the central nervous system (amphetamine-induced CTA learning or motor behavior), the behavioral effects of exposure to  $^{56}\text{Fe}$  particles are qualitatively different than the effects produced by exposure to  $^{60}\text{Co}$  gamma rays or fission spectrum neutrons. Behavioral effects observed following exposure to heavy particles are not observed following exposure to these other types of radiation ( $^{60}\text{Co}$  or  $n^0$ ). This means that the understanding of the effects of exposure to heavy particles on selected behavioral endpoints can only be determined by exposing organisms to heavy particles.

## ACKNOWLEDGMENTS

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